Review / Derleme

Selexipag: A New Treatment Agent for Pulmonary Arterial Hypertension

Selexipag: Pulmoner Arteriyel Hipertansiyon için Yeni Bir Tedavi Ajanı

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Abstract

Pulmonary arterial hypertension (PAH) is a rare disease which is characterized by the progressive increase of pulmonary arterial pressure. PAH can lead to right cardiac insufficiency and death. Conventional and other treatment modalities that target the physiopathological and etiopathological causes of the disease are currently being used. Selexipag is an oral selective prostacyclin receptor agonist which was developed to overcome the pathophysiological mechanisms that play role in the PAH.

Keywords
Pulmonary arterial hypertension, prostacyclin receptor agonist, novel theraphy

Öz

Pulmoner arteriyel hipertansiyon (PAH); pulmoner vasküler direnç ve arteriyel basınçta progresif artışla karakterize, sağ kalp yetmezliği ve erken ölüme neden olan nadir görülen bir hastalıktır. PAH tedavisi için geleneksel (konvansiyonel), hastalığın fizyopatolojisine yönelik, etiyopatolojiye yönelik ve diğer tedaviler kullanılmaktadır. Selexipag da PAH fizyopatolojisine yönelik geliştirilen güçlü, ağızdan kullanılabilen selektif prostasiklin reseptör agonistidir.

Anahtar Kelimeler
Pulmoner arteriyel hipertansiyon, prostasiklin reseptör agonist, yeni tedavi

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Introduction

Pulmonary hypertension (PH) is defined as having a mean pulmonary artery pressure ≥25 mmHg in the resting right cardiac pressure examination via catheterization. Pulmonary arterial hypertension (PAH) is a general description used in order to define progressive disorders that leads to right ventricular failure due to the increased pulmonary vascular pressure even the pulmonary capillary wedge pressure is in between normal range (1). PAH is a chronic and progressive disease and it is related to mortality and morbidity. The disease is characterized by the increase of pulmonary vascular resistance and this condition leads to overloading and hypertrophy in the right ventricle and early death (2,3). The processes that have been experienced in the search for the mechanisms related to the disease led us to the discovery of the drugs which target the 3 major pathways.

These pathways are prostacyclin, endothelin and nitric oxide pathways (3). Selexipag is a selective, long lasting, non-prostanoid, prostacyclin receptor agonist (4). Other drugs that affect the prostacyclin have a short half-life and they are administered by intravenous, subcutaneous or inhalation in general (5). There are some clinical trials to evaluate oral prostanoid and non-prostanoid IP receptor agonists in the treatment of PAH (Table 1). Selexipag was approved by the food and drug administration in December 2015 for using in the curative process of PH in order to delay the progress of the disease and to decrease the hospitalization risk (Figure 1) (6).

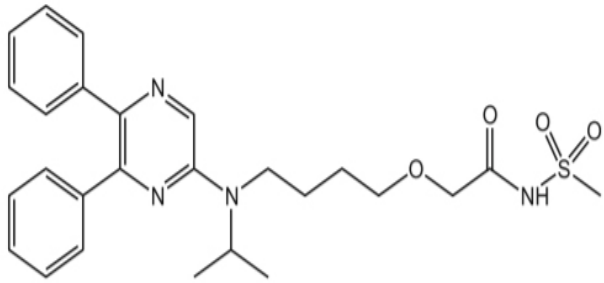

Figure 1. Structure of selexipag (6)

Table 1. Clinical trials examining oral prostanoid and non-prostanoid IP receptor agonists in the treatment of PAH

Trial	Study drug	n	Weeks	Background PAH therapy	Primary endpoint: treatment effect	Secondary endpoints
ALPHABET (12)	Beraprost	130	12	None	6 MWD: 25 meters, p=0.04	Progress in Borg dyspnea index versus placebo; no remarkable alteration in functional class, disease progression or hemodynamics
Beraprost study group (13)	Beraprost	116	52	None	Disease progression: placebo 17% versus beraprost 29%, p=0.254	No noticeable improvement in 12-month peak VO_2, Borg dyspnea index, 6 MWD, WHO functional class or hemodynamics
FREEDOM-C (15)	Treprostinil	350	16	100%	6 MWD: 11 meters, p=0.07	Development in dyspnea fatigue index score; no important difference in clinical deterioration, Borg dyspnea score, functional class
FREEDOM-C2 (16)	Treprostinil	310	16	100%	6 MWD: 10 meters, p=0.09	No remarkable chance in clinical deterioration, functional class, Borg dyspnea score, NT-proBNP, CAMPHOR
FREEDOM-M (17)	Treprostinil	349	12	None	6 MWD: 26 meters, p=0.01	No remarkable chance in Borg dyspnea score, functional class or symptoms of PAH
Selexipag phase 2 study (28)	Selexipag	43	17	100%	ΔPVR: -30%, p<0.01	Improvement in cardiac index; no remarkable chance in 6 MWD, Borg dyspnea score, NT-proBNP
GRIPHON (29)	Selexipag	1.156	64-71	80%	Disease progression: HR 0.6, p<0.001	Betterment in 6 MWD (12 meters, p<0.01) and NT-proBNP, no significant observation in proportion with worsening functional class

MWD: Minute walk distance, VO_2: Peak oxygen consumption, WHO: World Health Organization, NT-proBNP: N-terminal probrain natriuretic peptide, CAMPHOR: Cambridge Pulmonary Hypertension Outcome Review, PAH: Pulmonary arterial hypertension, PVR: Pulmonary vascular resistance, HR: Hazard ratio

Pharmacodynamics

IP receptor is one of the 5 prostanoid receptors. Prostacyclin induces the vasodilatation by activating IP receptor and inhibits the proliferation of vascular smooth muscles (6). It also has antithrombotic and anti-inflammatory effects (7,8). Selexipag acts similar to the endogenous PGI2. However; it is a non-prostanoid IP receptor agonist, not an analogue of PGI2 (5). Selexipag is more selective in terms of IP receptors compared to other prostanoid receptors, unlike prostacyclin analogues. This selectivity seen in selexipag against the IP receptors can minimalize the side effects derived from stimulation of other prostanoid receptors, thus increasing the tolerability of the selexipag. Several PGI2 analogues show a weak selectivity against IP receptors since they have a high affinity against prostaglandin E (EP) receptors. Selexipag is well tolerated and the gastrointestinal side effects are minimal since these side effects such as vomiting are related to the stimulation of EP-3 (9). Furthermore; side effects of the prostacyclin analogues are often related to the changes in the plasma levels of the drug. Since selexipag is hydrolyzed to its active metabolite in liver rapidly; the peak-through fluctuations of the active metabolite, thus the risk of side effects are decreased. Although selexipag and the active metabolite act like endogenous prostacyclins, they are different from the prostacyclins pharmacologically (10). Selexipag is hydrolyzed to its active metabolite (ACT-333679) via carboxylesterase 1. The active metabolite is 37 times more potent than the selexipag. ACT-333679 has 130 times higher affinity against the IP receptors compared to the prostacyclin receptors (6,11,12). Prolonged exposure of *in vitro* IP receptors with the PGI analogues (iloprost, beraprost and treprostinil) results in severe desensitization of these receptors (13-15). Therefore the dose needs to be increased in the treatment of PAH with PGI2 infusion. ACT-333679 does not result in desensitization or internalization of IP receptors. Consistent vasodilatation induced by the selexipag exposure does not decrease after the repeated doses. This finding indicates that selexipag is not related with severe IP receptor desensitization. Therefore it can be asserted that increasing the dose is less likely necessary in order to maintain the efficacy (16).

It was demonstrated that selexipag and the active metabolite inhibits the platelet aggregation dose-dependently (IC50 of 5.5 μM and 0.21 μM, respectively). However, any effect on the platelet aggregation wasn't seen with the dose range between 400-1800 mcg/2 times a day (6). Safety and efficacy of the selexipag were assessed in a proof-of-concept study conducted on PAH patients. The patients (class 2-3 according to the World Health Organization functional classification) that had been treating with fixed dose of endothelin receptor antagonist and/or phosphodiesterase type (PDE)-5 inhibitor were divided into 2 groups as selexipag and placebo users. The drug dose was increased to the maximum dose of 800 μg twice a day from the initial dose of 200 μg twice a day gradually. The study revealed that geometrical mean value of the pulmonary vascular pressure 30.3% decreased at the end of 17 weeks treatment [95% confidence interval (CI) -44.7 to -12.2%; p=0.0045]. Cardiac index was found as 0.41 L/min/m^2 (95% 0.10-0.71) increased in patients receiving selexipag. Selexipag was considered as safe in terms of the pharmacological effects and well tolerated (4). Selexipag didn't cause QT prolongation at the maximum dose of 1600 μg twice a day in healthy volunteers (11,17). In another study conducted on healthy volunteers assessing the interaction of selexipag and warfarin it was stated that selexipag didn't affect the pharmacodynamic effects of warfarin on international normalization ratio (11,18).

Pharmacokinetics

The pharmacokinetics of selexipag and its active metabolite are not affected by the severity of the disease and do not change in time. Selexipag and its active metabolite reach their maximum plasma concentration in 1-3 hours and 3-4 hours after taking orally, respectively (11). In a study of Kauffman et al. (19) it was stated that selexipag and its active metabolite reached their maximum plasma concentration in 2.5 and 4 hours respectively. In the same study; the mean half-life of selexipag and ACT-333679 were found in between 0.7-2.3 hours and 9.4-14.22 hours, respectively (6,19,20). Maximum bioavailability of selexipag is 49% in humans. This can be derived from the first-pass effect of selexipag (11). In preclinical studies conducted on monkeys, rats and dogs ACT-33679 were showed to have a high bioavailability (102% in rats and 80% in dogs). In the same study; it was also showed that ACT-333679 has a long half-life (3.6 hours in rats, 6.2 hours in dogs)

(21). The plasma near peak level of the ACT-333679 was found as more than 8 hours.

Oral use of selexipag concomitant with foods delays the absorption of selexipag causing a delay in the peak concentration and 30% decrease in the peak plasma concentration. It was indicated that concomitant use of selexipag with foods can result in a decrease of selexipag absorption and Cmax, delay in median Tmax levels compared to fasted state. It was also stated that exposure of selexipag wasn't affected by the presence of foods whereas exposure of its active metabolite was reduced by 27%. More adverse effects were reported in the fed state compared to fasted state (45% and 17% respectively). This shows that selexipag can be tolerated better when it is used with foods (11). Both selexipag and its active metabolite bind to plasma proteins after they are absorbed. Selexipag is converted to its active metabolite by hepatic carboxylesterase 1. The oxidative metabolism is catalyzed by CYP3A4 and CYP2C8 resulting in the production of hydroxylated and dealkylated products. UGT1A3 and UGT2B7 play role in glucuronidation of the active metabolite (6,11). The half-life of the selexipag is 0.8-2.5 hours and mean clearance is 35 L/h. The terminal half-life of the ACT-333679 is in between 6.2-13.5 hours allowing to be able to use twice a day (6). In a study of Kuwano et al. (16) about the single dose use of selexipag; half-life of the ACT-333679 was found as 7.9 hours. The drug is excreted mainly in feces and urine in a smaller amount. In a study conducted on healthy volunteers, fecal and urinary excretion of radioactive drug material were found as 93% and 12% respectively; However both the selexipag and ACT-333679 were not found in the urine (11). Metabolism of the selexipag and ACT-333679 are not affected by age, gender, ethnicity and weight. Dose adjustment is not necessary in patients with a glomerular filtration rate (GFR) above 15mL/min/1.73 m^2. Any clinical data exists about the dose of the drug in patients having a GFR value below this level. There is no need for dose adjustment in patients with mild hepatic insufficiency whereas decreasing the drug dose from twice a day to once in a day is recommended in patients with moderate hepatic insufficiency. There is not any clinical data about the use of the drug in patients with severe hepatic insufficiency and it is not recommended to use (6,11).

Clinical Studies About the Selexipag

A randomized, double-blind, multi-national, multi-centered, phase-2, proof-of-concept study was conducted by Simonneau et al. (4) in 2012 (NCT 00993408). This study was assessing the efficacy and safety of the selexipag in patients with PAH. In the study of Simonneau et al. (4), selexipag and placebo were randomized in the proportion of 3:1 in 43 adult patients with PAH. The etiology of the PAH in the aforementioned study includes idiopathic PAH, PAH-related connective tissue disorder, hereditary PAH, corrected congenital heart disease or anorexigen use related PAH. Patients had been using ERA and/or PDE-5 inhibitor during at least 12 weeks at a fixed dose. Selexipag dose had been increased from the initial dose of 200 µg twice daily to maximum tolerable dose of 800 µg twice daily in 35 days. Right cardiac catheterization had been performed at both the initiation and the end of the treatment. The geometric mean level pulmonary vascular pressure had been found as 30.3% decreased in selexipag group compared to placebo group at the end of 17 weeks of treatment (95% CI -44.7 to -12.2%; p=0.0045). The cardiac index had also been found as significantly increased (0.41 L/min/m^2, 95% 0.10-0.71) in selexipag group. Selexipag was considered as safe in terms of pharmacological effects and well tolerated (4).

GRIPHON study is a multi-national, multi-centered, double-blind, placebo-controlled phase-2 study (NCT01106014) and it investigates the efficacy and safety of the oral use of selexipag. It is the longest study that has been conducting about PAH. The study consists patients from 181 medical centers located in 39 countries located in North and Latin America, Europa, Pacific Asia and Africa. Patient admission was closed in May 2013 with the final population of 1156 patients. The results of the study were reported as the biggest randomized controlled study conducted on patients with PAH. 80% of the patients had been receiving ERA, PDE-5 or a combination of these two medications for the treatment of PAH. Patients were started on selexipag treatment with the initial dose of 200 µg twice daily and the dose was gradually increased to 1600 µg twice daily. Duration of the treatment was 70.7 and 60.7 weeks for selexipag and placebo, respectively. This important, event focused study was designed in order to assess if the first morbidity development or mortality is delayed or not

with the use of selexipag compared to placebo and to investigate the safety of selexipag. All the morbidity or mortality events reported by the investigators were evaluated by independent and blind critical event committee (22). A total of 1156 patients were treated in this global, long-term phase-3 study for 4.2 years. Development of morbidity or mortality (whichever takes place first) was found as 40% decreased in patients using selexipag compared to placebo (hazard ratio 0.60; 99% CI 0.46-0.78; p/0.001) (Figure 2). In GRIPHON study, general tolerability profile of selexipag was in accordance with prostacyclin

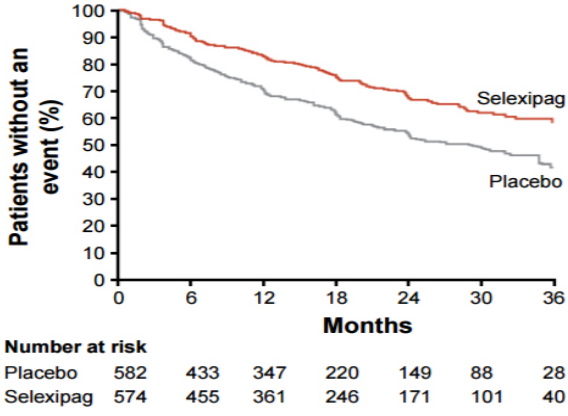

Figure 2. The effect of selexipag on mortality and morbidity in pulmonary arterial hypertension patients according to placebo (GRIPHON study) (2)

Table 2. Adverse events noticed during the GRIPHON clinical trial (2)

Adverse events	Placebo (n=577) (%)	Selexipag (n=575) (%)	p
Headache	189 (33	375 (65)	<0.001
Nausea	107 (19)	193 (34)	<0.001
Diarrhea	110 (19)	244 (42)	<0.001
Pain in jaw	36 (6)	148 (26)	<0.001
Vomiting	49 (9)	104 (18)	<0.001
Pain in extremit	46 (8)	97 (17)	<0.001
Dyspnea	121 (21)	92 (16)	0.03
Worsening of PAH	206 (36)	126 (22)	<0.001
Myalgia	34 (6)	92 (16)	<0.001
Peripheral edema	104 (18)	80 (14)	0.06
Dizziness	85 (15)	86 (15)	0.96

PAH: Pulmonary arterial hypertension

treatments. The length of 6 minutes of walking test was increased in patients using selexipag at the end of 26 weeks, whereas 9 minutes of walking test was found as decreased in patients using placebo (effect of the treatment, 12.0 m; 99% CI 1-24; p=0.003) (22).

Clinical Use and Adverse Effects

Recommended initial dose is 200 µg twice daily and the dose can be increased week by week up to the maximum tolerable dose of 1600 µg twice daily and the maintenance dose is decided based on tolerability. The initial dose is also 200 µg in patients with mild hepatic insufficiency and it can be increased 200 µg week by week based on the tolerability. There is no data about the dosing of selexipag in patients with severe hepatic insufficiency and it is not recommended to use. Dose adjustment is not necessary in patients with a GFR above 15 mL/min/1.73 m^2. Any clinical data exists about the dose of the drug in patients having a GFR value below this level (6,11). Selexipag was well tolerated in patients with PAH in the GRIPHON study. The adverse effects were similar with other prostacyclin analogues and these adverse effects were encountered during the dose titration, mostly. Incidence of serious adverse effects ≥1 were similar in placebo and selexipag group (47.1% and 43.8%, p=0.26 respectively). Headache, diarrhea, nausea, vomiting, mandibular pain, pain in the extremities, myalgia and flushing adverse effects were more common in selexipag group (Table 2). The ratios of patients who left the treatment due to the adverse effects were 14.3% and 7.1% in selexipag and placebo groups, respectively. The most common adverse effects that led the patients to left the treatment were headache (3.3%), diarrhea (2.3%) and nausea (1.7%). Hyperthyroidism was developed in 8 patients in patients on selexipag treatment and 1 patient left the treatment due to this reason (22). The risk of some catheter-related adverse effects that can be seen with the use of Prostaglandin analogues, such as embolism, thrombosis, infection and fluctuations in the received drug dose are decreased in selexipag since it is used orally. Therefore the safety and tolerability profile of the drug is better.

Conclusion

Selexipag is a long-lasting, selective, non-prostanoid oral prostacyclin receptor agonist. High

selectivity of the selexipag against IP receptors decreases the rate of adverse effects and helps the drug to be well tolerated. It is enough to use it since the half-life of its active metabolite is 7.9 hours. It can be asserted that selexipag is a good alternative of current prostacyclin analogues based on these superiorities. It is a promising candidate for oral combination treatment in PAH patients using the drugs that affect the major pathways.

Ethics

Peer-review: Externally peer-reviewed.

Authorship Contributions

Surgical and Medical Practices: O.Y., H.G., Concept: O.Y., Design: O.Y., H.G., Data Collection or Processing: O.Y., H.G., Analysis or Interpretation: O.Y., Literature Search: O.Y., H.G., Writing: O.Y.

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